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Journal
Biochimica et Biophysica Acta, 1840(8)

ISSN
0006-3002

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Publication Date
2014-08-01

DOI
10.1016/j.bbagen.2014.01.017

Peer reviewed

Published in final edited form as:
Biochim Biophys Acta. 2014 August ; 1840(8): 2520–2525. doi:10.1016/j.bbagen.2014.01.017.

Matrix regulators in neural stem cells functions

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Abstract

Background—Neural stem/progenitor cells (NSPCs) reside within a complex and dynamic extracellular microenvironment, or niche. This niche regulates fundamental aspects of their behavior during normal neural development and repair. Precise yet dynamic regulation of NSPC self-renewal, migration, and differentiation is critical and must persist over the life of an organism.

Scope of Review—In this review, we summarize some of the major components of the NSPC niche and provide examples of how cues from the extracellular matrix regulate NSPC behaviors. We use proteoglycans to illustrate the many diverse roles of the niche in providing temporal and spatial regulation of cellular behavior.

Major Conclusions—The NSPC niche is comprised of multiple components that include; soluble ligands, such as growth factors, morphogens, chemokines, and neurotransmitters, the extracellular matrix, and cellular components. As illustrated by proteoglycans, a major component of the extracellular matrix, the NSPC niche provides temporal and spatial regulation of NSPC behaviors.

General Significance—The factors that control NSPC behavior are vital to understand as we attempt to modulate normal neural development and repair. Furthermore, an improved understanding of how these factors regulate cell proliferation, migration, and differentiation, crucial for malignancy, may reveal novel anti-tumor strategies.

Keywords

Extracellular matrix; proteoglycan; HSPG; CSPG; Sulfs; sulfatases; neural progenitor; neural stem cell; NSC; tumor microenvironment

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1. Introduction

The patterning and development of the central nervous system (CNS) is a complex and highly organized process. In successive waves of proliferation, migration, and differentiation neural stem cells populate the CNS and give rise to neurons, astrocytes, and oligodendrocytes. During cortical neurogenesis, neural stem cells (neuroepithelial stem cells and subsequently radial glia cells slightly later in development) in the ventricular zone initially expand via symmetric division, and then shift toward an asymmetric division mode to give rise to intermediate progenitor cells [47, 94]. While the process of cortical gliogenesis is less well understood (see review [91]), the progenitor cells must also undergo tightly regulated self-renewal, migration, and differentiation. In the adult mammalian brain neural stem and progenitor cells persist and can participate in neurogenesis and gliogenesis under both normal and disease conditions [32, 103, 104]. Neural stem cells exist in the ventricular-subventricular zone, in the walls of the lateral ventricle, and in the subgranular zone, at the junction of the hilus and dentate gyrus [68, 125]. In addition, more differentiated oligodendroglial precursor cells (OPCs) reside in the brain parenchyma and can rapidly respond to injury [96, 123]. Through out life the behavior of neural precursor cells requires exquisite regulation.

Neural precursors reside within a complex and dynamic extracellular microenvironment, or niche. This niche regulates fundamental aspects of their behavior [5] and includes the brain extracellular matrix, blood vessels, microglia, and more differentiated neural cells (Figure 1). Extracellular factors such as growth factors, morphogens, chemokines, neurotransmitters, and the extracellular matrix are critical components of this niche. Indeed, extracellular cues are responsible for patterning of the nervous system and they generate critical domain-specific signals to radial glial cells that extend from the ventricular surface to the cortical pial surface during embryogenesis [94]. In this review, we focus on the factors present in the cellular microenvironment that regulate neural stem cells and their derived intermediate progenitor cells, collectively referred to as neural stem/progenitor cells (NSPCs). An understanding of how extrinsic cues regulate the spatial, temporal, and even subcellular signaling in NSPCs will improve our understanding of normal neural development and, as dysregulation of this process can lead to disease, may contribute to the development of novel therapeutic approaches to neurologic disease.

2. Components of the extracellular matrix of neural stem/progenitor cells

Diverse components make up the NSPC microenvironment, or niche, and many have the potential to regulate cell behaviors. Some of these components are reviewed below.

Growth factors, morphogens, chemokines, and neurotransmitters

Extracellular ligands, many of which are soluble, are a critical component of the regulatory network necessary for NSPC maintenance of self-renewal, differentiation, cell adhesion, and migration. Some of the many extracellular factors implicated in NSPC lineage specification and signaling include fibroblast growth factor (FGF), epidermal growth factor (EGF), stromal derived factor 1 (SDF1), sonic hedgehog (SHH), bone morphogenic protein (BMP), Notch, and GABA (see Table 1 and associated references).

Proteoglycans

Proteoglycans, consisting of a core protein and covalently attached glycosaminoglycan (GAG) chains, are present in the extracellular microenvironment and on the cell surface, often as GPI-linked or transmembrane proteins. Due to their structural complexity they can bind diverse extracellular factors, including signaling molecules, membrane proteins, and components of the extracellular matrix (ECM) [13]. As a result, proteoglycans play a vital role in cell-cell and cell-ECM signaling in the CNS. The most common types of proteoglycans in the brain contain heparan sulfate (HS), chondroitin sulfate (CS) or dermatan sulfate (DS) side chains. Another major constituent of the brain ECM is hyaluronan (or hyaluronic acid, HA). Composed of GAG chains without a protein core, HA is released from the cell where it interacts with ligands and matrix components and helps to regulate cell signaling [90]. On NSPCs HA binds a number of proteoglycans including neurocan (NCAN), aggrecan (ACAN), and versican (VCAN) [1].

Glycoproteins

Glycoproteins are a diverse group of proteins that contain one or more oligosaccharide chains (glycans) and they include integral membrane proteins, secreted extracellular proteins, and cytosolic proteins. Tenascin C (TNC) is an extracellular matrix glycoprotein that is highly expressed by NSPCs located in the brain and spinal cord during development and in the adult [42, 43, 63]. In the spinal cord, genetic ablation of TNC mediates deficits in the NSPC compartment resulting in sustained generation and delayed migration of astrocytes due to altered responsiveness to FGF2 and EGF [63]. Consistent with the dynamic interplay of factors within the NSPC niche, the TNC-mediated alterations in growth factor responsiveness may be due, in part, to secondary alterations in HSPGs [63].

Glycan binding proteins

Glycan binding proteins, divided broadly into lectins or glycosaminoglycan binding proteins, are thought to mediate many of the biologic functions of glycans [114]. For example, galectin-1, a lectin, promotes the proliferation of NSPCs in vivo and this phenotype is thought to be mediated via galectin-1 binding to glycans on β1 integrin [57, 100, 101].

Integrins

Cell adhesion to ECM is a critical component of the NSPC niche. The major cell surface receptors that mediate this interaction are the integrins. Due to their heterodimeric structure, consisting of α and β subunits, integrins are able to interact with a vast array of extracellular ligands, including collagens, laminin, fibronectin, vitronection, osteopontin, and transmembrane components such as E-cadherin. Many of these interactions are known to influence NSPC adhesion, migration, cell-cell communication, and cell survival (see review [108].

Basal lamina

The basal lamina is an important component of the NSPC niche. Enriched in laminin and collagen 1 [88], the basal lamina helps to regulate adhesion of NSPCs to the extracellular

matrix. In the adult, the basal lamina surrounds blood vessels and blocking α6β1 integrin from binding the laminin receptor resulted in decreased NSPC adhesion and altered proliferation [105]. Laminin also appears to regulate postnatal oligodendrocyte production in the ventricular-subventricular zone [99].

3. Proteoglycan regulation of neural stem and progenitor cell populations

Many NSPC behaviors are dependent on growth factor signaling (Table 1). HSPGs and CSPGs are highly expressed in the NSPC niche and they are known to modulate growth factor-mediated signaling [53, 70, 87]. Proteoglycan binding of extracellular ligands can have multiple effects on ligand bioavailability. Binding can sequester the ligand from degradation, establish morphogen gradients, and promote receptor activation by acting as a co-receptor [34]. Indeed, HSPGs stabilize the FGF ligand-receptor complex to promote FGF2 signaling [27, 35, 45, 67, 98, 122]. Proteoglycans can also regulate cell adhesion and cell migration through interactions with membrane proteins and other components of the ECM, including integrins, laminin, collagen, and fibronectin [70, 82]. In addition, proteoglycan intracellular functions are likely to contribute to NSPC regulation as they link extracellular signals with cytoskeletal organization and intracellular signaling [12, 33, 48, 81]. In the following discussion we use proteoglycans to illustrate how components of the cellular microenvironment regulate NSPC behavior. In addition, we use human disease phenotypes and data from experimental models to illustrate how a failure in the NSPC niche can lead to disease.

Heparan sulfate proteoglycans

HSPGs consist of a family of proteoglycans that include members that are primarily transmembrane (e.g. syndecans), GPI-linked to the membrane (e.g. glypicans), secreted from the cell (e.g. HSPG2), or reside in secretory vesicles (e.g. serglycin) [102]. Their ability to regulate growth factor signaling has been demonstrated in multiple systems and for multiple extracellular ligands. In murine embryonic stem cells (mESCs), HS chains help to drive neural precursor cell differentiation via promotion of FGF and BMP signaling [66]. Interestingly, promotion of BMP signaling is associated with a HS-mediated decrease in BMP degradation suggesting HS binding stabilizes or protects BMP ligand [66]. The syndecans (SDCs) include four members in mammals: SDC1-4. During cortical neurogenesis SDC1 is highly expressed in the NSPC niche where it promotes NSPC proliferation and progenitor cell maintenance, in part via its ability to promote Wnt signaling in NSPCs [118]. In other studies, SDC3 and SDC4 have been implicated in promoting neural cell migration [14, 83].

Perlecan (HSPG2) is a HSPG highly expressed in the basal lamina of the developing neuroepithelium and basal lamina surrounding blood vessels [92]. Mutations in the Drosophila homolog of HSPG2 cause defects in FGF and Hedgehog signaling to cause cell cycle arrest and prevents the onset of stem cell proliferation during early development in the fly {Park, 2003 #352, 120]. Similarly, genetic ablation of HSPG2 in the developing murine brain results in decreased Shh signaling, delayed cell cycle progression, and decreased progenitor cell differentiation [44]. Consistent with a role for HSPG2 in neural development, alterations in HSPG2 are associated with cephalic defects in mouse [6, 44] and in human

with poor development of the forebrain [7]. The growth factor binding ability of HSPG2, including to FGFs [8, 115] and Shh [95], is thought to be the primary mechanism by which HSPG2 regulates NSPC behavior.

The specificity and the affinity of HSPG-ligand interactions are largely determined by the HS chains and their sulfation pattern, particularly the 6O-sulfate (6OS) of glucosamine [15, 19, 34, 49, 62]. HS 6OS levels are regulated during biosynthesis and post-synthetically by the extracellular sulfatases (SULFs) [49, 93]. The Sulfs were first identified in the quail embryo based on their ability to promote Wnt signaling in myogenic progenitor cells [31]. Subsequent studies have demonstrated SULF regulation of diverse signaling factors, including Wnts, FGF2, vascular endothelial growth factor (VEGF), glial cell line-derived neurotrophic (GDNF), and stromal cell-derived factor 1 (SDF1) [3, 4, 28, 29, 31, 38, 39, 72, 112, 116]. Thus, it is likely that HS sulfation status in the NSPC niche helps to regulate crucial progenitor cell behaviors.

Indeed, alterations in HS sulfation can regulate NSPC differentiation. In the ventral spinal cord decreased HS sulfation, mediated by the Sulfs, is necessary for the Shh-mediated switch from generation of neural progenitors to oligodendroglial progenitors [17, 29, 109]. In contrast, embryonic stem cells with undersulfation of HS exhibit restricted differentiation potential and blocked neural lineage maturation [36]. The striking difference in cell response to decreased HS sulfation in these two systems can be attributed to differences in HS binding specificity and function for different signaling molecules. In the spinal cord, Shh signaling is required for differentiation and, decreased HS sulfation promotes Shh signaling potentially via release of sequestered ligand [109]. In embryonic stem cells, differentiation into neural cells requires FGF signaling and this signaling is promoted by sulfated HS [27, 35, 45, 67, 98, 122]. The 6O-sulfation levels of HS are also important in regulating signaling after neural injury. In a recent study, increased HS sulfation was shown to promote the formation of the glial scar [52], a process that inhibits CNS repair, and involves concomitant upregulation of CSPGs [16, 73].

Consistent with HS chains playing an important role in regulating ligand-mediated signaling in the brain, genetic alteration of HS chain synthesis results in abnormal brain phenotypes in mice [34, 82]. EXT1 (exostosin 1) and EXT2 (exostosin 2) encode glycosyltransferases which elongate HS chains and are essential for HS biosynthesis [78, 79, 85]. Conditional knockout of Ext1 in nestin-positive neural stem cells resulted in defects in neural patterning and cortical neurogenesis [56]. While multiple signaling pathways may be involved, the FGF pathway may be particularly important as Ext1-deficient neural stem cells exhibited reduced proliferation in response to FGF2 and FGF8 [56, 121].

In addition to their ability to regulate ligand-mediated signaling, HSPGs also play fundamental roles in cell-cell and cell-matrix interactions, including binding to integrins as described in the previous section, which in turn have important roles in the NSPC niche [9–11, 86].

Chondroitin sulfate proteoglycans

CSPGs are also abundantly expressed by NSPCs and have many known functions in ligand-mediated signaling, cell adhesion, and cell migration. Indeed, enzymatic removal of CS from NSPCs is associated with decreased proliferation in response to FGF2 and altered differentiation in response to EGF [106]. In embryonic OPCs PTPRZ1, a transmembrane proteoglycan that can be modified by CS and DS, acts to maintain self-renewal and suppress differentiation [84]. Another proteoglycan, which has been widely studied to have many functions in OPCs, is the transmembrane proteoglycan CSPG4/NG2. Highly expressed on OPCs, CSPG4/NG2 promotes OPC proliferation and migration [40, 46, 69] (for review see [111]). Using mice lacking the *cspg4* gene, it has been shown that CSPG4/NG2 promotes proliferation of platelet-derived growth factor receptor alpha (PDGFRA)-positive OPCs and its absence confers delays in mature oligodendrocyte production [69]. In combination with binding studies demonstrating high affinity binding sites for FGF2 and PDGFAA on CSPG4/NG2 [46], it has been suggested that CSPG4/NG2 may act as a reservoir or co-receptor for these growth factors. In addition, direct interactions between CSPG4/NG2 and the receptor tyrosine kinase (RTK) itself can promote mitogenic signaling, as has been observed for FGFR1 and FGFR3 in pericytes and smooth muscle cells [23].

In OPCs CSPG4/NG2 is also a marker of polarity and regulates EGF-dependent proliferation and self-renewal [107]. As CSPG4/NG2 is required to set-up OPC polarity, CSPG4/NG2 may actively participate in regulating asymmetric progenitor divisions, a fundamental process to maintaining progenitor populations in the brain [107]. In addition, CSPG4/NG2 can functionally interact with diverse ECM components [20], including $\alpha 3\beta 1$ integrins [40] and carbohydrate binding proteins (lectins) [40, 119], which, as already described, are important components of the NPSC niche. As with HSPGs, sulfation of CS chains is a critical determinant of function, and knockdown of CSPG biosynthetic enzymes have demonstrated defects in cell migration from the ventricular zone into the cortical plate [58].

Another major constituent of the developing brain and of the adult NSPC niche is hyaluronan (or hyaluronic acid, HA). The physiologic role for HA is diverse due to both its range in size, from a small number of disaccharide units to an extensive high molecular weight polysaccharide, and its ability to interact with multiple extracellular molecules, including hyalectins, neurocan, aggrecan, versican, and lectican present in the NSPC niche [1, 60]. Hyaluronan can also block the differentiation of progenitor cells in the brain [37] and promote activation of RTK signaling pathways including ERBB2 and PDGFRB [90]. Its function in the NSPC niche has been recently reviewed [97].

4. Conclusions

The development and repair of the central nervous system requires both precise and dynamic regulation of NSPCs that must persist over the life of the organism. The extracellular microenvironment, or niche, is complex. There are many cellular components, such as endothelial cells, ependymal cells, more differentiated neural cells, astrocytes, and microglia. There are soluble ligands, including growth factors, morphogens, chemokines, and neurotransmitters, and there are the many components of the extracellular matrix.

Together these components make up the NSPC niche and act to regulate fundamental behaviors of NSPCs. In this review we use proteoglycans to illustrate ways in which the niche can regulate NSPC behavior. An improved understanding of how extrinsic cues regulate NSPC behavior is critical and may contribute to advances in stem/progenitor cell-based therapies, improved repair from CNS injury, and potentially novel therapies for neoplastic diseases in the brain including glioblastoma.

Acknowledgments

This work was supported by the National Institutes of Health (R01 NS081117 to JJP) and the James S. McDonnell Foundation (J.J.P.). We apologize to the many investigators whose articles we did not cite due to space constraints.

Abbreviations

NSPC	neural stem/progenitor cell
HSPG	heparan sulfate proteoglycan
CSPG	chondroitin sulfate proteoglycan
EGF	epidermal growth factor
FGF	fibroblast growth factor
Shh	sonic hedgehog
BMP	bone morphogenic protein
OPC	oligodendroglial precursor cells

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Highlights

- NSPCs reside in a complex extracellular microenvironment or niche
- The extracellular matrix is a major component of the NSPC niche
- Proteoglycans have diverse roles in the niche
- The NSPC niche harbors many potential therapeutic targets for neurologic disease

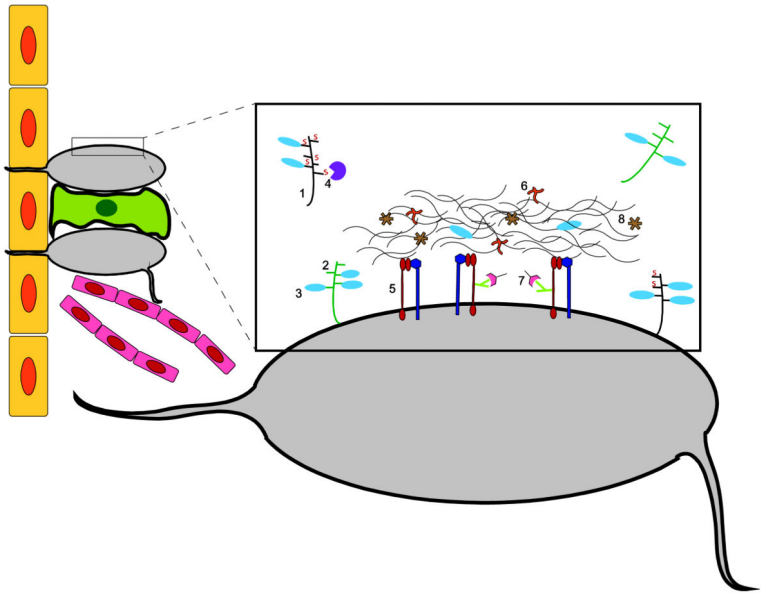

Figure 1. Extracellular matrix components within the neural stem/progenitor cell (NSPC) niche

In the adult NSPC niche in the wall of the lateral ventricle, NSPCs (grey) are in close proximity with ependymal cells (yellow), cerebrospinal fluid, blood vessels (pink) and more differentiated neural cells (green). There is also a diverse extracellular matrix (inset). Heparan sulfate (1) and chondroitin sulfate proteoglycans (2) are present either at the plasma membrane, attached via a transmembrane domain or a GPI-link, or are secreted. At the plasma membrane proteoglycans can sequester ligands (3) to alter local ligand concentrations or prevent degradation, promote RTK signaling by acting as co-receptors, promote cell adhesion by interacting with the extracellular matrix and with integrins (5), and facilitate cell migration. In the extracellular environment proteoglycans can be enzymatically modified to generate soluble, biologically active fragments and the SULFs (4) remove 6O-sulfates from HS. Integrins (5) facilitate cell-extracellular matrix adhesion in the NSPC niche through direct interactions with extracellular components including laminin (6), glycan binding proteins (7) and glycoproteins such as tenascin C (8). Figure is not to scale.

Table 1

Extracellular factor	Commonly reported role in NSPCs	Reference
BMP	Differentiation, dorsal morphogen; quiescence	[41, 77, 89]
EGF	Proliferation at onset of gliogenesis	[21, 76]
FGF1 and FGF2	Proliferation	[76, 113]
GABA	Differentiation, decreased proliferation	[80, 110, 117]
Noggin	Proliferation, blocks BMP	[77]
Notch	Inhibit neuronal differentiation; maintenance	[2, 24, 25, 30, 55]
PDGF-AA	Proliferation of NSPC early and OPCs later in development	[50]
SDF1	Recruitment to vasculature, adhesion and motility	[64, 105]
SHH	Proliferation; ventral specification; determinant of cell fate	[18, 51, 54, 71, 124]
VEGF	Proliferation; neurogenesis	[22, 59, 74]
VCAM	Adhesion, maintenance	[65]
Wnt	Self-renewal	[26, 61, 75]